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Reversal of chemoresistance and enhancement of apoptosis by statins through down-regulation of the NF-κB pathway

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ABSTRACT

We recently found that simvastatin can modulate the nuclear factor-κB (NF-κB) activation pathway, but whether other statins have similar effects to those of simvastatin is unknown. Therefore, we evaluated the effect six different statins on TNF-induced NF-κB activation in human myeloid leukemia cells. We then determined whether the combination of statins and standard chemotherapeutic agents could overcome chemoresistance and augment apoptosis. Of the six statins evaluated, only the natural statins (simvastatin, mevastatin, lovastatin, and pravastatin), not the synthetic statins (fluvastatin and atorvastatin), inhibited TNF-induced NF-κB activation. Simvastatin suppressed the NF-κB activation and potentiated the apoptosis induced by doxorubicin, paclitaxel, and 5-fluorouracil. These results suggest that different statins behave differently from one another and that they may be useful in overcoming chemoresistance.

1. Introduction

Statins may be the most important family of cholesterol-lowering drugs to emerge in the 21st century [1]. Statins primarily inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is needed to produce cholesterol through the mevalonate pathway.

Recent evidence suggests that statins have pleiotropic effects and thus may be useful in the treatment of diseases such as cancer [2–6]. Indeed, statins have been found to have anticancer activity in various cancer cell types, including colorectal [7], colon [8], bladder [9], prostate [10], and gastrointestinal [11] cancer, although they do not significantly reduce the risk for breast, prostatic, colorectal, or lung cancer [12]. Browning and Martin [13] suggested that statins are not associated with short-term cancer risk, but longer latency effects are possible.

Recently, we reported that simvastatin can potentiate the TNF-induced apoptosis through down-regulation of nuclear factor-κB (NF-κB) regulated antiapoptotic gene products [14]. NF-κB activation has been associated with tumor cell proliferation, invasion, angiogenesis, and metastasis through its regulation of various gene products [15]. Thus, NF-κB suppression in cancer cells may be useful in the prevention and treatment of cancer [16]. Inducible drug resistance has emerged as a substantial obstacle to effective cancer therapy, and NF-κB activation may play a role in the development of chemoresistance [17]. In fact, chemotherapeutic agents themselves can activate NF-κB, which leads to tumor cells' eventual resistance to therapy [17]. NF-κB activation has been associated with paclitaxel, doxorubicin, and 5-fluorouracil resistance in tumor cells [18–20].

Lovastatin, mevastatin, simvastatin (a methyl derivative of lovastatin), and pravastatin are natural statins, isolated from

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Abbreviations: NF-κB, nuclear factor-κB; TNF, tumor necrosis factor α; EMSA, electrophoretic mobility shift assay.

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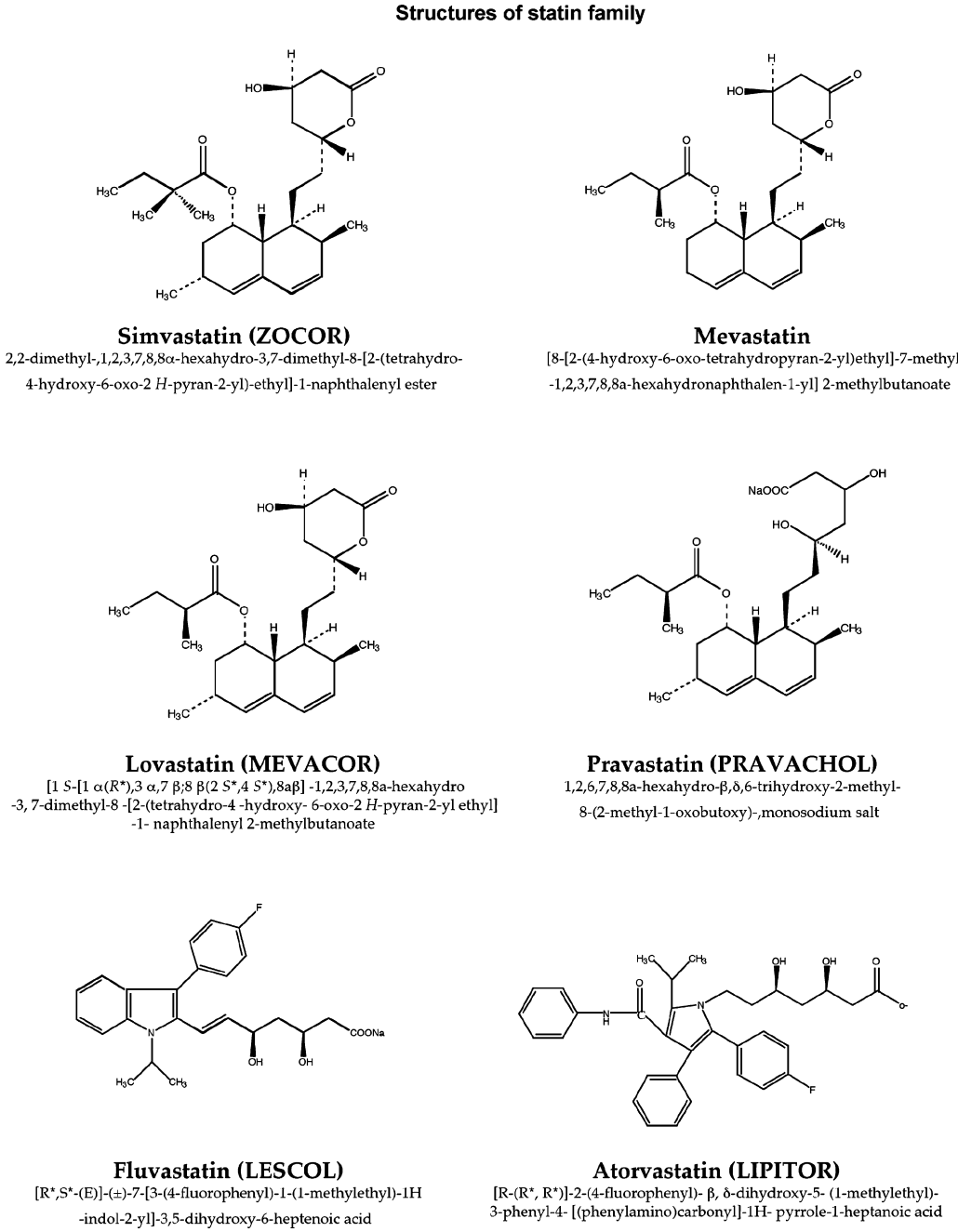

Fig. 1 – Structures of the natural (lovastatin, mevastatin, simvastatin, and pravastatin) and synthetic (fluvastatin, atorvastatin) statins used.

fermented red yeast rice; fluvastatin, atorvastatin, cerivastatin, rosuvastatin, and pitavastatin are synthetic compounds. Natural and synthetic statins have different biologic characteristics (Fig. 1); whether they have similar potency against NF-κB and can potentiate the effects of chemotherapeutic agents is not understood. Therefore, we examined the ability of six statins to suppress TNF-induced NF-κB activation and if this inhibition overcomes chemoresistance and enhances apoptosis in human myeloid leukemia cells. The six statins varied in their ability to suppress NF-κB activation, and simvastatin suppressed chemotherapeutic agent-induced NF-κB activation, leading to potentiation of apoptosis.

2. Materials and methods

2.1. Materials

All statins were obtained from LKT Laboratories, Inc. (St. Paul, MN). A 50 mM solution of statins was prepared in 100% dimethyl sulfoxide, stored as small aliquots at −20 °C, and then diluted as needed in cell culture medium. Bacteria-derived recombinant human tumor necrosis factor (TNF), purified to homogeneity with a specific activity of 5×10^7 U/mg, was kindly provided by Genentech (South San Francisco, CA). Penicillin, streptomycin, Iscove's modified Dulbecco's